PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
103364601/SAH		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE99/01688	24.09.1999	24.09.1998
International Patent Classification (IPC) or national classification and IPC7		
A 61 K 9/16, A 61 K 31/445		
Applicant		
Diabact AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.04.2000	16.01.2001
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Authorized officer Henrik Nilsson/EÖ Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE99/01688

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-12 , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the claims:
pages _____ , as originally filed
pages 13-15 , as amended (together with any statement) under article 19
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the drawings:
pages 1 , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☐ the sequence listing part of the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE99/01688

III. Non-establishment f pinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 19-20

because:

☐ the said international application, or the said claims Nos. 19-20
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE99/01688

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-18	YES
	Claims		NO
Inventive step (IS)	Claims	1-18	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-18	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The invention relates to a pharmaceutical composition for the treatment of acute pain by sublingual administration. The composition comprises an essentially water-free "ordered mixture" of fentanyl or a pharmaceutically acceptable salt thereof, in the form of microparticles, which are adhered to the surface of carrier particles. The carrier particles are substantially larger than the fentanyl particles, and are essentially water-soluble. The composition also comprises a bioadhesion or mucoadhesion promoting agent mainly adhered to the surfaces of the carrier particles.

The International Search revealed the following documents of particular relevance:

A. EP324725 A1
B. EP144243 A1
C. Farrar JT et al. J Natl Cancer Inst 90 (1998), 611-616 (MEDLINE-abstract)

Document A discloses an essentially water-free composition comprising an ordered mixture of water-soluble particles and significantly smaller particles of the active substance. The active substance particles adhere to the surface of the carrier particles. In the composition disclosed in document A, the concentration of active substance is 0.4-5% by weight. The active substance particles are smaller than 10 µm in diameter and the carrier particles have a diameter of 100-500 µm. The carrier particles consist of mannitol or lactose and therefore fragmentize easily when compressed, for instance in the manufacture of tablets. The carrier particles also comprise up to 25% modified cellulose gum, which functions as disintegrant and facilitates dissolution of the carrier particles and

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

release of the active substance. However, in the pharmaceutical composition disclosed in document A, fentanyl is not used as active substance, and the document only discloses oral, not sublingual, administration of the composition. Furthermore, no surfactant has been used in the composition known through document A. Cellulose gum has been used in document A, however without disclosing its function as a bioadhesion agent. In document A, the cellulose gum is evenly distributed in the carrier particles, thus being present on the surfaces of the carrier particles as well as inside the particles.

Document B discloses sublingual administration of the analgesic substance buprenorphine.

Document C discloses oral transmucosal administration of a salt of fentanyl for treatment of acute pain.

None of the documents revealed in the International Search relate to sublingual administration of an ordered mixture of fentanyl. Furthermore, the documents do not suggest the use of a bioadhesion or mucoadhesion agent mainly adhered to the surfaces of the carrier particles. Particular advantages, such as reduced erratic drug absorption, are obtained by the pharmaceutical composition of the present invention. Thus, claims 1-18 are considered to fulfil the requirements of novelty, inventive step and industrial applicability.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01688

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/16, A61K 31/445
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0324725 A1 (KABIVITRUM AB), 19 July 1989 (19.07.89) --	1-23
A	EP 0144243 A1 (RECKITT AND COLMAN PRODUCTS LIMITED), 12 June 1985 (12.06.85) --	1-23
A	Dialog Information Services, File 154, MEDLINE, Dialog accession no. 09481986, Medline accession no. 98213107, Farrar JT et al: "Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients"; J Natl Cancer Inst (UNITED STATES) Apr 15 1998, 90 (8) p 611-6 --	1-23

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2000	22 -01- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson/ELY Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/01688

Claims 21-23 relates to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compound(s)/composition(s).

Replaced by Article 19

Claims

1. A pharmaceutical composition for the treatment of acute pain by sublingual administration, comprising an essentially water-free, ordered mixture of microparticles of fentanyl or a pharmaceutically acceptable salt thereof adhered to the surface of carrier particles, wherein said carrier particles are substantially larger than said microparticles of fentanyl and are essentially water-soluble.

2. A composition according to claim 1, comprising from 0.05 to 20 weight percent of fentanyl.

3. A composition according to claim 1 or 2, comprising from 0.05 to 5 weight percent of fentanyl, preferably then from 0.1 to 1 weight percent.

4. A composition according to any one of claims 1-3, wherein the particles of fentanyl have a weight based mean diameter of less than 10 μm.

5. A composition according to any one of claims 1-4, wherein the mean sieve diameter of the carrier particles is less than 750 μm, preferably then from 100 to 600 μm.

6. A composition according to any one of claims 1-5, wherein the carrier comprises a brittle material which will fragmentize easily when compressed.

7. A composition according to any one of claims 1-6, which comprises a bioadhesion and/or mucoadhesion promoting agent.

8. A composition according to claim 7, wherein the carrier particles contain from 0.1 to 25 weight percent of the bio/mucoadhesion promoting agent, preferably then from 1 to 15 weight percent, based on the total composition.

9. A composition according to claim 7 or 8, wherein the bio/mucoadhesion promoting agent is selected from the group consisting of acrylic polymers, cellulose derivatives, natural polymers having mucoadhesive properties, and mixtures thereof.

10. A composition according to claim 9, wherein the bio/mucoadhesion promoting agent is selected from the group consisting of cellulose derivatives and comprising hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, microcrystalline cellulose and modified cellulose gum; crosscaramellose; modified starch; acrylic polymers comprising carbomer and its derivatives; polyethylene oxide; chitosan; gelatin; sodium alginate; pectin; scleroglucan; xanthan gum; guar gum; poly-co-(methyl vinyl ether-maleic anhydride); and mixtures thereof.

11. A composition according to any one of claims 1-10, further comprising a pharmaceutically acceptable surfactant in a finely dispersed form and intimately mixed with the fentanyl.

12. A composition according to claim 11, wherein the surfactant is present in an amount from 0.5 to 5 weight percent of the composition, preferably then 0.5 to 3 weight percent.

13. A composition according to claim 11 or 12, wherein the surfactant is selected from the group consisting of sodium lauryl sulfate, polysorbates, bile acid salts and mixtures thereof.

14. A composition according to any one of claims 1-13, wherein the carrier particles comprise a water-soluble, pharmaceutically acceptable carbohydrate and/or inorganic salt.

15. A composition according to claim 14, wherein the carrier particles comprise one or more of the materials mannitol, lactose, calcium phosphate and sugar.

16. A composition according to any one of claims 1-15, wherein the carrier particles contain at least one pharmaceutical disintegrating agent promoting the dispersion of the microparticles of fentanyl over the sublingual mucosa.

17. A composition according to claim 16, wherein the disintegrating agent is selected from the group consisting of cross-linked polyvinylpyrrolidone, carboxymethyl starch, natural starch, microcrystalline cellulose, cellulose gum, and mixtures thereof.

18. A composition according to claim 16 or 17, wherein the disintegrating agent is present in an amount from 1 to 10 weight percent of the composition.

19. The use of fentanyl or a pharmaceutically acceptable salt thereof in microparticle form for the preparation of an essentially water-free pharmaceutical composition for the treatment of acute pain by sublingual administration, wherein the microparticles are adhered to the surfaces of carrier particles which are substantially larger than said microparticles and are essentially water-soluble.

20. The use according to claim 19, wherein a bioadhesion and/or mucoadhesion promoting agent is included in the composition.

21. A method for the treatment of acute pain, wherein to an individual afflicted with acute pain is administered sublingually at least one dose unit of an essentially water-free pharmaceutical composition containing an effective amount of fentanyl or a pharmaceutically acceptable salt thereof in the form of microparticles adhered to the surfaces of carrier particles, which are substantially larger than said microparticles and are essentially water-soluble.

22. A method according to claim 21, wherein a bioadhesion and/or mucoadhesion promoting agent is included in the composition.

23. A method according to claim 21 or 22, wherein the fentanyl is adminstered in an amount from 0.05 to 20 mg, preferably then from 0.1 to 5 mg, per dose unit.